EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

NAFAMOSTAT FOR THE TREATMENT OF COVID-19

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Monitoring Report

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**14/08/2020**	First version, search includes grey literature and contacts with authors and trial investigators
V 2.0	**15/09/2020**	Second version

Major changes from previous version

Chapter, page no.	Major changes from version 1.0
Tables 4-1 and 4-2, p. 12-13	• More trials, planned and ongoing, have been added

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
ITT	Intention-to-treat
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PP	Per Protocol
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/services/covid-19/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Nafamostat (nafamostat mesylate, no ATC code) is a synthetic trypsin-like serine protease inhibitor (https://pubchem.ncbi.nlm.nih.gov/compound/Nafamostat) on the market in Japan and South Korea as generic drug for intravenous use.
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

1. Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects

model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: http://deplazio.net/farmacicovid/index.html for SoF (or https://covid-nma.com/)

2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis using the following sources:

- https://www.fhi.no/en/qk/systematic-reviews-hta/map/
- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info

Population	See project Scope
Intervention	Nafamostat drug treatment
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Prospective non-randomised controlled trials, prospective case series, registries Exclusion criteria: retrospective case series, case studies

One researcher carries out title and abstract screening and assesses the full texts of all potentially eligible studies. One researcher extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25).

Results are presented in tabular form for all included studies.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher is searching and extracting the data for the eligible studies.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

To enter into airway epithelial cells, coronaviruses rely on host cell proteases for activation of the viral protein involved in membrane fusion [4, 5]. The transmembrane protease, serine 2 (TMPRSS2) [6], has been shown to facilitate viral entry of the coronaviruses SARS-CoV, HCoV-NL63 and MERS-CoV in cells engineered to overexpress TMPRSS2. Trypsin-like serine protease inhibitors, camostat and nafamostat, inhibited viral entry [7-9]. At a dose of 30mg/kg, camostat caused survival in 60% of the mice in a lethal SARS-CoV BALB/c mouse model [10].

When SARS-CoV-2 emerged, loss- and gain-of-function experiments identified TMPRSS2 as a key mediator of cell infection through virus-cell fusion [11]. In addition to coronaviruses, TMPRSS2 and the structurally similar serine protease, human airway trypsin-like protease, have been linked to influenza virus activation. Active site inhibitors of these airway proteases (e.g. camostat and nafamostat) might thus have broad therapeutic applicability [4, 12].

The SARS-CoV-2 virus enters cells via its spike protein, first binding to the cell-surface enzyme ACE2. Then the spike protein is cleaved by furin at the S1/S2 site followed by cleavage by TMPRSS2 at the S2′ site. This triggers a conformation change that 'primes' the spike protein for fusion of the viral and cellular membranes, releasing the virus genome into the host cell. This process can be inhibited by either blocking furin or TMPRSS2 [13]. Note that these requirements differ from those of viral spreading through cell-cell fusion. Unlike ACE2, TMPRSS2 does not appear to exert a cytoprotective role. Inhibiting the function of TMPRSS2 may therefore not exert adverse effects [14].

Camostat, its active metabolite GBPA/FOY 251 [11, 15], and nafamostat [15] directly inhibit TMPRSS2 enzymatic activity. This has been confirmed in a molecular dynamics and Markov model study, in preprint [16]. All three molecules were also shown to inhibit the activation and cellular entry of SARS-CoV-2 [11, 17-19].

3.2 Regulatory Status

Nafamostat mesilate (FUT-175, Futhan®, Nichi-Iko Pharmaceutical) is, like camostat, a trypsin-like serine protease inhibitor. Nafamostat 10mg for injection is on the market in Japan since 1986 for acute symptoms of pancreatitis; 50mg for injection is marketed since 1989 for disseminated intravascular coagulation and prevention of coagulation of perfused blood during extravascular circulation of patients with bleeding lesions or bleeding tendencies. Nafamostat is a serine protease inhibitor (with implications on coagulation, fibrinolysis, complement system, inflammatory cytokine release) and is quickly hydrolysed, the reason why it is typically administered as an intravenous drip. Meanwhile, multiple companies market nafamostat generics in Japan and South Korea (e.g. Futhan, SK Chemicals). Nafamostat is not approved for any use by EMA or FDA.

Sun Pharma in India has initiated manufacturing both the API and the finished product of nafamostat in India using technology from its subsidiary, Pola Pharma Japan [20]. Different initiatives are ongoing to prepare an oral formulation with or without slow release characteristics. For example, Ensysce in the US is developing different routes of administration of nafamostat through its subsidiary Covistat, including the oral and inhaled route (www.covistat.com). Nafamostat is also being developed for inhaled use in Japan by University of Tokyo, RIKEN, Nichi-Iko and Daiichi Sankyo [21], and in Germany, funded by the German federal ministry of education and research (BMBF) [22].

3.3 Level of Evidence

Until now, no scientific publication on randomized clinical trials of nafamostat in Covid-19 patients could be identified.

In South Korea, three Covid-19 pneumonia patients over 65 years, requiring oxygen and progressing despite treatment with HCQ and lopinavir/ritonavir, improved and could be discharged after intravenous administration of 200 mg daily of nafamostat for 4 to 13 days followed by oral camostat 3x200mg daily for 4 days [23]. Four more cases were treated successfully afterwards (personal communication 28/5/2020 by Dr. Ji-Young Rhee, corresponding author).

At Tokyo University hospital, 11 severely ill patients received nafamostat plus favipiravir. Ten out of 11 patients could be discharged [24]. In one patient, hyperkalaemia was reported (preprint at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7412297/).

In Japan, more Covid-19 patients have been treated off-label with nafamostat. Bleeding, including microbleeding in the brain, should be considered as a possible side-effect as nafamostat is a short acting anticoagulant [25].

A successful outcome in a case of severe respiratory failure was described after combination treatment of HCQ plus iv nafamostat in Japan (preprint by Iwasaka et al., available from https://www.sciencedirect.com/science/article/pii/S1341321X20302713).

4 SUMMARY

There is a sound scientific rationale to investigate nafamostat in Covid-19 clinical trials. Such trials are currently ongoing.

Table 4-1 Ongoing trials of single agent nafamostat

Active substance	**Nafamostat**				
Sponsor	Gyeongsang University, South Korea	Padova University, Italy	Edinburgh ad Oxford University, UK	Sun Pharma, India	Pasteur Institute, Dakar, Senegal
Trial Identifier	KCT0005003	NCT04352400	NCT04473053; ISRCTN14212905	CTRI/2020/06/026220	NCT04390594
Phase & Intention	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2
Study design	1:1 randomized open label RCT	1:1 randomized placebo-controlled RCT	1:1:1 randomized single blind RCT	1:1 randomized open label RCT	1:1 randomized open label RCT
Status of trial	planned	planned	recruiting	recruiting	planned
Duration/End of Study					
Study details					
Number of Patients	2x42 patients	2x128 patients	3x20 patients, 100 patients?	2x20 patients	2x93 patients
Disease severity					
Setting	hospital	hospital	Community? hospital	hospital	hospital
Location/Centres					
Intervention drug name and dosage	Nafamostat 0.1 to 0.2mg/kg/hr (2.4 to 4.8mg/kg/day) for 10-14 days based on disease severity	Nafamostat iv	Nafamostat 0.2mg/kg/hr for 7 days	Nafamostat 0.1 mg/kg/hr for 10 days	Nafamostat 0.1 to 0.2mg/kg/hr for 10-14 days based on disease severity
Comparator (drug name and dosage)	Standard of care	Placebo	Inhaled TD139; standard of care	Standard of care	Standard of care
Duration of observation/ Follow-up					
Primary Outcomes	7 point clinical scale	7 point clinical scale	Safety	Clinical improvement	Viral load day 7

Abbreviations: RCT=randomized controlled trial

Table 4-2 Ongoing trials of combination therapies nafamostat

Active substance	**Nafamostat**
Sponsor	Tokyo University, Japan
Trial Identifier	JPRN-jRCTs031200026
Phase & Intention	Phase 2
Study design	RCT
Status of trial	Not reported
Duration/End of Study	
Study details	
Number of Patients	2x80 patients
Disease severity	
Setting	hospital
Location/Centres	
Intervention drug name and dosage	Nafamostat iv + favipiravir tablets
Comparator (drug name and dosage)	Favipiravir tablets
Duration of observation/ Follow-up	
Primary Outcomes	Fever, SpO2, and chest image findings, PCR
Results/Publication	

Abbreviations: RCT=randomized controlled trial

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